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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,722	07/10/2006	Rosanne M Crooke	BIOL0004USA	6604

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,722	CROOKE ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61,65-70,72-76 and 84-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61, 65-70, 72-76, and 84-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Remarks filed January 31, 2008.

Claims 61, 65-70, 72-76, and 84-99 are pending.

Claims 61, 65-70, 72-76, and 84-99 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

In the previous Office Action mailed February 14, 2007, claims 61, 65-70, and 72-76 were provisionally rejected under the judicially created doctrine of double patenting over claims 23, 38, 39, 45-62 and 64 of copending Application No. US Publication No. 20040208856 ('856). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed February 14, 2007.

Response to Arguments

In the response filed on August 14, 2007, Applicants requested that this rejection be held in abeyance until the claims are otherwise in a condition for allowance. This request has been considered and it is noted that that this rejection will be held in abeyance until the claims are found to be allowable.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed October 31, 2007, claims 61, 65-70, 72-76, and 84-99 were rejected under 35 U.S.C. 103(a) as being unpatentable over Shachter,

N. (Applicant's Reference BF on the Information Disclosure Statement filed August 14, 2007), in view of GenBank Accession No. NT_035088 (Applicant's Reference BL on the Information Disclosure Statement filed August 14, 2007), Jong et al. (Arterioscler Thromb Vasc Biol., 1999 Vol. 19:472-484), Senior, K. (Drug Discovery Today, 2002 vol. 7:840-841, Applicant's Reference BE on the Information Disclosure Statement filed August 14, 2007), and Monia et al. (Applicant's Reference AE on the Information Disclosure Statement filed August 14, 2007). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed October 31, 2007.

Response to Arguments

In response to this rejection, Applicants argue that none of the cited references, either alone, or in combination suggests to the artisan of ordinary skill that antisense compounds 100% complementary to SEQ ID NO:4 should be used in methods for ameliorating hepatic stenosis or lowering liver tissue triglyceride levels in an animal. This argument has been fully considered, but is not found persuasive because firstly, KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396).

Applicants contend that in view of the Supreme Court's recent decision in KSR *Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007), the PTO must identify an explicit reason to combine the elements of the prior art in the manner defined by the claims. This

contention has been fully considered, but is not found persuasive because in the previous Office Action mailed October 31, 2007, the Examiner identified why the artisan of ordinary skill would be motivated to combine the elements of the prior art to arrive at Applicant's invention. For example, and in short, Jong and Shachter were relied upon primarily to teach the desire to inhibit Apo-CIII at the gene level. For example, Jong explicitly teach, "Changes in human APOC gene expression may play an important role in the etiology of human hyperlipidemias". Shachter explicitly teach, "[V]ariation in the expression of ApoC-III has been credibly documented to have an important role in hypertriglyceridemia" (see Abstract). Shachter goes on to teach the use of the fibrate class drugs and certain statins to vary or reduce ApoC-III expression and subsequently decrease triglyceride concentrations (see paragraph bridging pages 298 and 299). While Jong and Shachter do not explicitly teach that antisense agents are used to vary the expression of ApoC-III, Senior teach the desire to develop antisense drugs that complement statin therapies (see page 841, middle column). Therefore, using these teachings, it would be obvious that an artisan of ordinary skill would design an antisense oligonucleotide as a drug that functions to vary or reduce ApoC-III expression.

In addition, Senior was relied upon primarily to teach an expectation of success in administering to an animal, an antisense compound that specifically hybridizes with a nucleic acid molecule encoding a lipoprotein. While it is true that Senior does not mention antisense compounds that are 100% complementary to ApoC-III specifically, it is the Examiner's position that an artisan of ordinary skill could take the successful teachings of Senior and apply them with a reasonable expectation of success in

combination with Jong and Shachter, N. and GenBank Accession No. NT_035088 to arrive at Applicant's invention.

Applicants next argue that Senior does not cure the deficiencies of Jong and Shachter since Senior discloses antisense compounds that specifically hybridize to ApoB. Applicants contend that although ApoB and ApoC-III are both involved in lipid metabolism, the two are distinct genes and nothing in Senior suggests to the artisan of ordinary skill that antisense compounds that specifically hybridize to ApoC-III could achieve reduced liver triglyceride levels as instantly claimed.

This argument and contention have been fully considered, but are not found persuasive because Applicant is reminded that the test for obviousness is not whether the features of the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375. Applicant argues against the Senior reference individually, but must consider the rejection based upon the combination of the references. See MPEP 2145. As discussed *supra*, Senior was relied upon primarily to teach an expectation of success in administering to an animal, an antisense compound that specifically hybridizes with a nucleic acid molecule encoding a lipoprotein. While it is true that Senior does not mention antisense compounds that hybridize to ApoC-III specifically, it is the Examiner's position that an artisan of ordinary skill could take the successful teachings of Senior

and apply them with a reasonable expectation of success in combination with Jong and Shachter and GenBank Accession No. NT_035088 to arrive at Applicant's invention.

Applicants next argue that the teachings of Monia offer nothing regarding the effects of apolipoprotein C-III expression on hepatic stenosis or liver triglyceride concentrations. Applicants argue that with respect to GenBank Accession No. NT_035088, nothing is provided to teach reduction of cholesterol or triglyceride concentration, treatment of delay of hypertriglyceridemia, or therapeutic modulation of apolipoprotein C-III expression. Applicants argue that in this regard, combining Monia or GenBank Accession No. NT_035088 with the remaining references in no way cures the deficiencies discussed above.

This argument has been fully considered, but is not found persuasive. First, and as discussed *supra*, Applicant argues against the Monia and GenBank Accession No. NT_035088 references individually, but must consider the rejection based upon the combination of the references. See MPEP 2145. As discussed in the previous Office Action mailed October 31, 2008, in combination, the references render the instant claims legally obvious over Shachter, N., in view of GenBank Accession No. NT_035088, Jong et al., Senior, K. and Monia et al.

Second, it appears that Applicants are arguing limitations not found in the instant claims. It is noted that Applicants discuss that nothing is provided to teach reduction of cholesterol or triglyceride concentration, treatment or delay of hypertriglyceridemia, or therapeutic modulation of apolipoprotein C-III expression. However, nowhere is “reduction of cholesterol” or “treatment or delay of hypertriglyceridemia" recited in

Applicant's claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants next argue that the teachings of Senior, Jong, Shachter, Monia and GenBank Accession No. NT_035088 even in combination, fail to provide an artisan of ordinary skill with a reasonable expectation of practicing the claimed methods. Applicants contend that Shachter merely indicates that ApoC-III plays a role in lipid metabolism and fails to teach even a single link between reducing ApoC-III expression and reducing liver triglyceride levels or treating or ameliorating hepatic steatosis in an animal. Applicants also contend that Senior discusses antisense modulation of ApoB, a completely different gene product from ApoC-III. Applicants argue that in view of these deficiencies coupled with the complete lack of guidance in Senior, Jong, and Shachter regarding, for example, selection of a therapeutic antisense compound specifically hybridizable to SEQ ID NO:4 for use in treating the recited disorders, Senior, Jong, and Shachter fail to provide a reasonable expectation of success.

These arguments and contentions have been fully considered, but are not found persuasive because Shachter clearly teaches that reducing ApoC-III reduces triglyceride levels. For example, Shachter teaches that drugs belonging to the fibrate class reduce apoC-III gene expression and have a triglyceride-lowering effect (see paragraph bridging pages 298 and 299). The fact that reducing ApoC-III subsequently reduces triglyceride levels is also acknowledged by Applicants in their arguments filed January 31, 2008 at page 5, third full paragraph where Applicants disclose, "At best,

therefore, Shachter teaches that drugs that can achieve reduced triglyceride concentrations can also modulate apolipoprotein C-III expression".

Regarding Applicant's argument that there is a complete lack of guidance in Senior, Jong, and Shachter for selection of a therapeutic antisense compound specifically hybridizable to SEQ ID NO:4 for use in treating the recited disorders, this is found unpersuasive. Senior explicitly discloses, "[D]eveloping antisense drugs depends very much on identifying an appropriate target" (see page 840, first column). It is noted that this criteria has been fully met and satisfied since GenBank Accession No. NT_035088 relied upon in the instant rejection comprises a nucleotide sequence that code for human apolipoprotein C-III. Senior also explicitly discloses, "[A]ntisense technology, by contrast, is a *successful approach* [emphasis added] because the oligonucleotides that match the sequence of the gene stop translation of the mRNA in the liver" (see page 840, second and third columns). Thus, given the teachings of Senior, the artisan of ordinary skill could easily take the identified target provided by GenBank Accession No. NT_035088, design antisense that match the sequence of the gene to subsequently stop translation of the mRNA, which would in turn lead to the identification and selection of therapeutic antisense agents 100% complementary to SEQ ID NO:4 for use in treating the disorders recited in the claims. Therefore, the combined teachings of Senior, K. and GenBank Accession No. NT_035088 provide one of ordinary skill in the art would a reasonable expectation of success to practice the methods as claimed.

Applicants next argue that assuming *arguendo* that the cited combination of references might make it "obvious to try", KSR forecloses any conclusion of obviousness for the methods as presently claimed. Specifically, Applicants contend that assuming *arguendo* that Shachter might teach that decreasing expression of ApoC-III might be effective in methods for reducing cholesterol or triglyceride concentrations, neither Shachter nor Senior teach or suggest that antisense compounds specific for SEQ ID NO:4 as opposed to any other available strategy should be used in the methods as claimed. It is noted that Applicants argue that other available strategies include a myriad of options including a number of fibrate class drugs, statins, and other drugs provided in Exhibit A, which is the Physician's Desk Reference listing a number of other drugs for the treatment of hyperlipidemia.

This argument and contention have been fully considered, but are not found persuasive because Shachter teach that statin drugs can achieve reduced triglyceride concentrations and can modulate ApoC-III expression (see paragraph bridging pages 298 and 299). Senior teaches generally that antisense oligonucleotides can be used to reduce gene expression of an appropriate target, such as a gene involved in lipid metabolism. Senior also teaches the desire to develop, specifically, antisense drugs that complement statin therapies (see page 841, second column). Therefore, given the combined teachings of Shachter and Senior, combined with the teachings of GenBank Accession No. NT_035088, amongst the myriad of options available, one of ordinary skill in the art would be motivated to use antisense compounds 100% complementary to

SEQ ID NO:4 in a method of reducing triglyceride levels, for example, as recited in Applicant's claimed invention.

Therefore, in view of the previous Office Action mailed October 31, 2007, the evidence of record shows that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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tcg
May 8, 2008

/Sean R McGarry/

Primary Examiner, Art Unit 1635

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/553,722	CROOKE ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	